Feeding the Kidneys in AKI: No appetite for a change in practice

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The quest for the "silver bullet" to protect kidney function in critical illness has been largely unsuccessful over the last decades. Most of these "negative" clinical investigations concentrated on selective increases of renal blood flood (RBF) and glomerular filtration rate (GFR) using adenosine agonists, natriuretic peptides, prostaglandins, renal dose dopamine ([1] or just recently fenoldopam [2].

Infusion of amino acids (AA) has been demonstrated to improve both RBF and GFR in animal experiments [3] as well as in some pilot trials in humans [4] [5]. In the current issue Doig and colleagues [6] present an original and interesting, well designed and executed multicenter phase II randomized controlled trial (RCT) investigating the effect of daily infusion of AA on kidney function in a cohort of 474 critically ill patients. Patients with expected intensive care unit (ICU) stay of more than 2 days were randomly assigned to standard care or daily IV supplementation with up to 100g AA (adapted to achieve a protein intake of 2g/kg/d) in addition to standard nutrition. The renal effects of the intervention were limited to a statistically significant increase of eGFR (with a peak difference of 7.7 ml/min/1.73m^2) and urinary output (by an average of 300 ml/d), compensating the increased fluid intake. The primary outcome, i.e. duration of renal dysfunction, defined as the number of days (corrected for time at risk) with a serum creatinine above 168 μmol/L (1.9mg/dL) was, however, not different between control and treatment groups. The same was true for other clinically significant outcomes such as use of renal replacement therapy (RRT), mortality, length of stay and days of mechanical ventilation.

Scientifically the study proves an ancient physiological concept in nephrology that intravenous administration of AA results in an increased RBF and GFR. This aspect, also known as "renal functional reserve", simply represents the capacity of the normal kidney to adapt to an increased protein or amino acid load. The underlying mechanism remains largely speculative but is thought to include changes in glomerular hemodynamics due to more afferent than efferent vasodilation, potentially explained by AA-sodium cotransport resulting in decreased distal sodium delivery with reduced activation of the tubuloglomerular feedback [7]. Hormonal effects mediated by glucagon, insulin like growth factor -1 or growth hormone have also been implicated [8]

The concept of an increase of GFR with infusion of AA is used to establish renal reserve in candidates for living kidney donation. As such it could also be a useful approach to determine susceptibility to acute kidney injury (AKI). The fact that Doig and colleagues could demonstrate an increased eGFR with AA administration indicates that also critically ill patients are capable of activating their renal reserve [6]. The crucial question, however, remains whether activation of renal reserve in the critically ill confers to improved clinical outcome. The negative effect on the primary outcome (i.e. duration of renal dysfunction) would suggest that this is not the case. Although one would presume that an improvement of RBF should be protective against AKI, studies in sepsis-associated AKI, the most predominant form of AKI in the critically ill, indicate a limited pathophysiological role for RBF. Indeed, animal models of sepsis show a reduced GFR with enhanced rather than diminished RBF [9]. This lead some authors to hypothesize that a reduced GFR may be even protective for the kidney by reducing oxygen demand and filtration of tubular toxins [10-12]. In addition, a recent animal model of sepsis showed an increased renal vascular resistance and decreased RBF and GFR after an AA infusion [13]. However, pathophysiology AKI may be profoundly different in sepsis as compared to other causes like cardiac surgery. Unfortunately, the authors do not provide a discrimination of the effects of AA infusion on various aetiologies of renal dysfunction. Finally, in chronic kidney disease induction of hyperfiltration by protein load has turned out rather detrimental resulting in a more rapid progression of CKD [14]

Besides the questionable value of increasing GFR in critically ill patients, the improvement of eGFR achieved by AA acid infusion was moderate (amounting to a peak difference of 7,7 ml/min/1.73m^2 on day 4) and presumably too small to have a clinical impact. Measured with a cystatin-based equation, the eGFR difference was even smaller. This limitation is further substantiated by the fact that neither the duration of impaired renal function nor the requirement for RRT could be influenced by AA infusion. RRT even tended to be instituted more frequently with AA infusion, possible triggered by higher blood urea nitrogen (BUN) values resulting from increased AA metabolism. At initiation of RRT other parameters of kidney function (potassium, urine output, pH, serum creatinine) were not worse or even better in the treatment arm, suggesting that the BUN levels may indeed have driven the decision to start RRT. In addition, after controlling for baseline differences, the trend towards increased need for RRT disappeared.

A major shortcoming of this paper is the definition of renal dysfunction. The authors missed to apply more up-to-date criteria for the definition of AKI (e.g. KDIGO)[15] and, thus, it is conceivable that effects on lower stages of AKI remained undetected due to the definition used in the present study applying a fixed cut-off of serum creatinine to define "renal dysfunction". Using a modern AKI definition based on changes in serum creatinine in comparison with the level at inclusion might have been a better approach to demonstrate an effect on prevention of AKI.

Besides the renal aspect, this trial is also the first RCT comparing guideline-suggested amounts of proteins with higher doses. Current recommendations suggest a daily protein administration of 1.5 g/kg body weight [16, 17] although some authors support doses up to 2.0-2.5 g/kg [18]. By adding AA infusion to standard nutrition Doig and colleagues applied protein doses up to 2,5 g/kg/d. Furthermore, energy provision, which was around 1100 kcal/day in the control group, increased to roughly 1300 kcal/day with AA infusion. Despite the increased caloric and protein intake none of the parameters expected to be influenced by a successful nutritional intervention could be improved. Length of stay, duration of mechanical ventilation, rate of infection, pressure ulcers or quality of life and physical function in 90-day survivors did not show any difference between the two groups. The only measured effect was increased ureagenesis, confirming results from the EPaNIC trial [19] .

All together the results of this trial show us that activation of renal reserve by additional AA infusion is feasible in critically ill patients. Whether this intervention is also renoprotective is far less clear. Its clinical benefit appears at least questionable and future trials, when deemed appropriate, should use modern, more sensitive definitions of AKI, preferably include renal biomarkers and focus on specific subsets of critically ill patients reflecting different pathophysiologies of AKI.

Conflict of interests
The authors declare that they have no conflict of interests regarding this publication.

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